



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2016-N-2896]

Public Meeting on Pre-Market Evaluation of Abuse-Deterrent Properties of Opioid Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public meeting; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public meeting to discuss scientific and technical issues relating to formulation development and pre-market evaluation of opioid drug products with abuse-deterrent properties. The meeting is intended to give FDA the opportunity to discuss, and seek public input from stakeholders on, the approach to testing FDA recommended in its draft guidance “General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products.” The meeting will also provide an opportunity to discuss FDA’s efforts to develop standardized in vitro testing methodologies for evaluating the abuse deterrence of opioid drug products. FDA is seeking input from all stakeholders, including patients, health care providers, health care payers, the pharmaceutical industry, patient advocates, academics, researchers, and other government entities.

FDA may hold one or more additional meetings in the future to discuss the risk-benefit paradigm for opioid drug products to ensure that FDA is appropriately considering the full public health impact of prescription opioid drug products and the post-market impact (“real world effects”) of abuse-deterrent opioid drug products.

DATES: The public meeting will be held on October 31, 2016, from 8:30 a.m. to 4:30 p.m. and November 1, 2016, from 8:30 a.m. to 4 p.m. The meeting may be extended or end early depending on the level of public participation. Individuals seeking to attend or to present at the meeting must register by October 17, 2016. Please register here for the meeting:

<http://www.cvent.com/d/wvq0sm/4W>. Electronic or written comments regarding scientific and technical issues relating to formulation development and pre-market evaluation of abuse-deterrent properties of opioid drug products will be accepted until December 1, 2016.

ADDRESSES: The public meeting will be held at College Park Marriott Hotel and Conference Center, 3501 University Blvd. East, Hyattsville, MD 20783.

You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see “Written/Paper Submissions” and “Instructions”).

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2016-N-2896 for “Public Meeting on Pre-Market Evaluation of Abuse-Deterrent Properties of Opioid Drug Products.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its

consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:

<http://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FDA will post the agenda approximately 3 days before the public meeting at: <http://www.fda.gov/Drugs/NewsEvents/ucm509853.htm>. FDA will also post a link to the live Webcast of this public meeting on the day of the public meeting.

FOR FURTHER INFORMATION CONTACT: Michelle Eby, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 6184, Silver Spring, MD 20993, 301-796-4714, Michelle.Eby@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Prescription opioid analgesics are an important component of modern pain management. Prescription opioid analgesic products such as oxycodone, hydrocodone, and morphine, are widely prescribed for the treatment of pain, and certain opioid drug products are also used in opioid dependence treatment programs. When used properly, opioid drug products can provide significant benefits for patients. Unfortunately, misuse and abuse of opioid drug products is a serious public health problem.

When misused or abused, opioid drug products can cause serious harm, including addiction, overdose, and death. According to the Centers for Disease Control and Prevention (CDC), prescription opioid drug products were involved in over 14,000 deaths in 2014.¹ FDA is determined to help defeat this epidemic through an adaptive, science-based approach.

In February 2016, FDA announced a comprehensive action plan to take concrete steps toward reducing the impact of opioid abuse on families and communities.² As part of this plan, FDA strongly supports the development of, and transition to use of, opioid drug products with meaningful abuse-deterrent formulations. FDA has taken and is continuing to take steps to incentivize and support the development of opioid drug products with progressively better abuse-deterrent properties. These steps include working with individual sponsors on promising abuse-deterrent technologies, publishing guidance on the evaluation and labeling of abuse-deterrent drug products, and conducting and supporting research in developing appropriate pre-market testing methodologies for evaluating the abuse deterrence of both innovator and generic drugs.

¹ Wide-Ranging Online Data for Epidemiologic Research (WONDER), National Center for Health Statistics; available at <http://wonder.cdc.gov>.

² <http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm>

FDA believes abuse-deterrent technologies can and will improve substantially and can make a real impact in the fight against prescription opioid abuse. FDA hopes that as the market transitions to abuse-deterrent formulations, abuse rates will decrease and the most significant consequences of that abuse (addiction, overdose, and death) will diminish. To that end, fostering the development, marketing, and iterative improvement of abuse-deterrent formulations of opioid drug products, including generic opioid drug products, is a top priority. It is important that generic versions of opioids that reference approved opioids whose labeling describes abuse-deterrent properties are available to help ensure widespread access to safe and effective analgesics for patients who need them and to accelerate the prescribing of abuse-deterrent opioids. Such generic opioids should be no less abuse-deterrent than the opioids they reference; otherwise opioid abusers could preferentially seek out and abuse easier-to-abuse generics.

FDA's work to date to support the development, marketing, and iterative improvement of abuse-deterrent formulations includes:

- Holding a public meeting in October 2014 to discuss the "Development and Regulation of Abuse-Deterrent Formulations of Opioid Medications;"
- Issuing a final guidance in April 2015 on the "Abuse-Deterrent Opioids--Evaluation and Labeling." This guidance explains FDA's current thinking about the studies, both pre- and post-marketing, that should be conducted to demonstrate that a given formulation for which a new drug application (NDA) is submitted has abuse-deterrent properties. It also makes recommendations about how those studies should be performed and evaluated and what information about a product's abuse-deterrent properties should be included in labeling;

- To date, approving seven opioid analgesic drug products with labeling describing abuse-deterrent properties³ consistent with the final guidance on evaluation and labeling of abuse-deterrent opioids;
- Seeking guidance from outside experts in the fields of pain management and drug abuse. For example, FDA has asked the National Academies of Sciences, Engineering, and Medicine to help develop a framework for opioid drug product review, approval, and monitoring that balances individual needs for pain control with the risk of addiction, as well as the broader public health consequences of opioid drug product misuse and abuse;
- Conducting or supporting research on opioid drug product formulations designed to deter abuse. This includes development of in vitro testing methodologies to assess purportedly abuse-deterrent formulations; and
- Issuing a draft guidance on the “General Principles for Evaluating Abuse Deterrence of Generic Solid Oral Opioid Drug Products.”

In the notice of availability for the draft guidance on evaluating abuse deterrence of generic opioid drug products, FDA announced its intent to hold a public meeting following the close of the comment period to discuss further the pre-market evaluation of the abuse deterrence of generic opioid drug products and related issues, as appropriate. FDA is opening a docket and holding this public meeting to further discuss pre-market evaluation of the abuse deterrence of generic opioid drug products and the development of standardized in vitro testing methodologies for evaluating the abuse deterrence of opioid drug products.

³ A list of opioid medications with FDA-approved labeling describing abuse-deterrent properties can be found at <http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm514939.htm>.

Day 1 of this meeting will focus on scientific and technical issues related to the pre-market evaluation of the abuse deterrence of generic opioid drug products. It is important to have a viable pathway for approval of generic abuse-deterrent opioid drug products to further FDA's goal to transition to abuse-deterrent formulations as FDA looks forward to a future in which all or substantially all opioid medications are less susceptible to abuse than the formulations on the market today. The availability of generic versions of opioid drug products that reference listed drugs whose labeling describes abuse-deterrent properties can help to ensure access to safe and effective, and affordable, opioid analgesics for patients who need them.

Day 2 will focus on FDA's efforts to develop standardized in vitro testing methodologies for evaluating the abuse deterrence of opioid drug products. In vitro testing should, to the greatest extent possible, provide information sufficient to fully characterize a drug product's abuse-deterrent properties, including the degree of effort required to bypass or defeat those properties. In vitro studies should assess each potential route of abuse (including ingestion, injection, insufflation, and smoking) starting with simple and gentle mechanical and chemical manipulations progressing to complex and more destructive manipulations until a drug product's abuse-deterrent properties are defeated or compromised. To be sufficiently comprehensive, in vitro testing should address both the mechanisms by which abusers can be expected to attempt to deliberately overcome the abuse-deterrent properties of the product as well as the ways that patients may alter the formulation (intentionally or unintentionally) that change the rate or amount of drug released.

A. Day 1: FDA's Evaluation of Generic Abuse-Deterrent Opioids

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) (FD&C Act) permits any person to submit to the FDA an abbreviated new drug application (ANDA) to

seek approval to market a generic version of a previously approved drug product. To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug. Instead, the applicant relies on FDA's finding that a previously approved drug product, i.e, the reference listed drug (RLD), is safe and effective, and must demonstrate, among other things, that the proposed generic drug is the "same" as the RLD in certain ways and is bioequivalent.

For FDA to approve an ANDA, the Agency must find, among other things, that the generic drug product has the same active ingredient(s), dosage form, route of administration, strength, conditions of use, and, with limited exceptions, labeling as the RLD, is bioequivalent to its RLD, that the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are adequate to assure and preserve its identity, strength, quality, and purity, and that the inactive ingredients and composition of the generic drug are not unsafe under the conditions of use prescribed, recommended, or suggested in the labeling. See section 505(j)(2)(A) and (j)(4) of the FD&C Act.

FDA classifies as "therapeutically equivalent" those products that meet the following general criteria: (1) They are approved as safe and effective; (2) they are pharmaceutical equivalents in that they contain identical amounts of the same active ingredient(s) with the same route of administration and dosage form and meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent; (4) they are adequately labeled; and (5) they are manufactured in compliance with current good manufacturing practices regulations. See FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book), Preface. FDA believes that a product classified as therapeutically equivalent

can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the reference product.

If the RLD's labeling describes properties that are expected to deter misuse or abuse then the potential ANDA applicant should evaluate its proposed generic drug product in comparative in vitro studies and, in some cases, in relevant pharmacokinetic or other studies to show that it is no less abuse-deterrent than the RLD with respect to all potential routes of abuse.⁴

It is important that generic versions of opioid drug products referencing opioid drug products with FDA-approved labeling describing abuse-deterrent properties are available to help ensure availability of analgesics for patients who need them. FDA is interested in supporting the submission of ANDAs for which the RLD is an opioid drug product whose labeling describes abuse-deterrent properties and ensuring that generic opioid drug products are no less abuse-deterrent than the RLD in its efforts to combat the opioid epidemic.

Topics for discussion during the open public comment period on Day 1 and by the panel:

- Based on any testing you have attempted to perform or performed in accordance with the March 2016 draft guidance, are there any aspects of the guidance that need clarification or improvement?
- Are there any characteristics of the currently approved abuse-deterrent RLDs for which issuance of product specific guidance, beyond what is described in FDA's March 2016 draft guidance, would facilitate development of abuse-deterrent generic opioid drug products?

⁴ FDA's current thinking regarding the labeling of opioids is described in FDA's guidance for industry on "Abuse-Deterrent Opioids--Evaluation and Labeling" (April 2015). Any data relating to abuse-deterrent properties would be included in the DRUG ABUSE AND DEPENDENCE section of product labeling, 9.2 Abuse.

- Are there approaches or technologies for evaluating the abuse deterrence of generic opioid drug products that were not included in the March 2016 draft guidance that should be?
- What additional actions could FDA take to encourage the submission of ANDAs that reference an opioid drug product whose labeling describes abuse-deterrent properties?
- Are there potential consequences of the development and introduction of abuse-deterrent opioid drug products that warrant further consideration?

B. Day 2: Development of Standardized In Vitro Testing to Evaluate Abuse Deterrence

The Office of Pharmaceutical Quality (OPQ) will discuss its vision for standardizing in vitro testing methodologies for evaluating purportedly abuse-deterrent formulations of opioid drug products. OPQ will also discuss the efforts being made to standardize in vitro testing conditions to apply to future products and some of the challenges being encountered. OPQ's Office of Testing and Research will then provide an update on its testing of abuse-deterrent formulations, including approaches being taken to simulate the ways individuals who abuse opioids manipulate opioid drug products for purposes of abuse (e.g., crushing, heating, dissolving). FDA recognizes that new technologies for deterring abuse of oral opioid drug products are rapidly evolving and is seeking public input on novel mechanisms and approaches being considered so that it may further consider how testing could be standardized.

FDA intends to issue a general guidance describing FDA's recommendations for standardized in vitro testing to evaluate purported abuse-deterrent properties and considerations for a potential applicant as it develops an abuse-deterrent formulation of an opioid drug product. Building on the testing FDA has conducted and other available information including public input, FDA may recommend common protocols that incorporate standard test conditions,

specified performance standards, control formulations and provide a tiered approach for determining when abuse-deterrent properties have been defeated and how that information may be used during drug development and for other relevant comparative situations. The guidance also may describe lifecycle considerations (e.g., the need for testing abuse deterrence throughout shelf life to determine if any product changes over time affect abuse-deterrence performance) and provide additional guidance on evaluating novel technological approaches used to deter abuse of oral opioid drug products.

Topics for discussion during the open public comment period on Day 2 and by the panel:

- What technical and quantitative issues should FDA consider as it develops guidance to recommend standardization of in vitro testing to evaluate the abuse deterrence of opioid drug product formulations for various routes of abuse, including ingestion, insufflation, injection, and smoking? For example, what should FDA consider with respect to mechanical manipulations (e.g., equipment, amount of effort, and time), chemical manipulations (e.g., solvent choice and availability), particle size distribution, and volume of solvent used for extraction?
- How can FDA standardize in vitro testing to help substantiate appropriate and consistent product manufacture that assures abuse deterrence at release and through a drug product's shelf life?
- How can performance attributes measured by in vitro testing be quantified and linked to their impact on abuse deterrence? For example, discuss what amount of time delay in defeating an abuse-deterrent property should be considered significant and the basis for the recommendation.

- How can FDA build flexibility into standardized testing so that it may be suitable for application to emerging technologies? Are there any specific emerging technologies that might require new types of testing?

II. Registration and Accommodations

Registration: Registration is free and available on a first-come, first-served basis.

Persons interested in attending this public meeting must register by close of business on October 17, 2016.

If you need special accommodations because of a disability, please contact La'Shaune Morant, 240-316-3206, email: lashaune@tepgevents.com no later than October 12, 2016.

To register for the public meeting, please visit <http://www.cvent.com/d/wvq0sm/4W> (FDA has verified the Web address, but FDA is not responsible for subsequent changes to the Web site after this document publishes in the Federal Register) by October 17, 2016. Those without Internet access may register by contacting La'Shaune Morant, 240-316-3206. Early registration is recommended because facilities are limited and, therefore, FDA may limit the number of participants from each organization. You will receive confirmation after you have registered and been accepted or you will be notified if you are on a waiting list. FDA may allow onsite registration if space is available. If registration reaches maximum capacity, FDA will post a notice closing registration at <http://www.fda.gov/Drugs/NewsEvents/ucm509853.htm>.

Streaming Webcast of the Public Meeting: The meeting will also be Webcast. Persons interested in viewing the Webcast must register online by October 17, 2016. Early registration is recommended because Webcast connections may be limited. Organizations are requested to register all participants, but to view using one connection per location. A link to the live Webcast will be available at <http://www.fda.gov/Drugs/NewsEvents/ucm509853.htm> on the day

of the public meeting. A video record of the public meeting will be available at <http://www.fda.gov/Drugs/NewsEvents/ucm509853.htm> following the meeting. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

Requests for Oral Presentations: If you wish to present at the public meeting, you must register and indicate which topic(s) you wish to address: approach to testing FDA recommended in its draft guidance “General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products,” new technologies for deterring abuse of oral opioid drug products, or standardization of in vitro testing methodologies for evaluating purportedly abuse-deterrent formulations of opioid drug products. This will help FDA organize the presentations. FDA will do its best to accommodate requests to make public comments. Individuals and organizations with common interests are urged to consolidate or coordinate their presentations, and request time for a joint presentation. Following the close of the registration, FDA will determine the amount of time allotted to each presenter and the approximate time each oral presentation is to begin, and will select and notify participants by October 24, 2016. All requests to make oral presentations must be received by the close of registration, October 17, 2016. If you are selected, any presentation materials must be emailed to Michelle Eby (see FOR FURTHER INFORMATION CONTACT) no later than October 27, 2016. No commercial or promotional material will be permitted to be presented or distributed at the public meeting.

FDA is holding this public meeting to obtain information on scientific and technical issues relating to formulation development and pre-market evaluation of opioid drug products with abuse-deterrent properties. In order to permit the widest possible opportunity for public comment, FDA is soliciting either electronic or written comments on all aspects of the public

meeting topics. The deadline for submitting comments related to this public meeting is December 1, 2016.

Accommodations: Attendees are responsible for their own hotel accommodations. Attendees making reservations at the College Park Marriott Hotel and Conference Center, 3501 University Blvd. East, Hyattsville, MD 20783, are eligible for a reduced rate of \$231/night, not including applicable taxes. To receive the reduced rate, please reference “FDA Opioid Drug Meeting” if you make your reservation by calling 1-800-676-6137, or book your reservation at http://www.marriott.com/meeting-event-hotels/group-corporate-travel/groupCorp.mi?resLinkData=FDA%20Opioid%20Drug%20Meeting%5Ewasum%60FDGFDGA%60231.00%60USD%60false%602%6010/30/16%6011/1/16%6010/12/16&app=resvlink&stop_mobi=yes.

If you need special accommodations because of a disability, please contact La’Shaune Morant, 240-316-3206, lashaune@tepgevents.com no later than October 12, 2016.

III. Transcript Request

Transcripts of the meeting will be available for review at the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20850, and on the Internet at <http://www.regulations.gov> approximately 30 days after the meeting. A transcript will also be available in either hard copy or on CD-ROM, after submission of a Freedom of Information request. The Freedom of Information office address is available on the Agency’s Web site at <http://www.fda.gov>.

Dated: September 30, 2016.

Leslie Kux,

Associate Commissioner for Policy.